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TITLE: Stabilization of tetanus toxoid in poly(DL-lactic-co-

glycolic acid) microspheres for the controlled release of

antigen.

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Sustained release of antigenically active tetanus toxoid (TT) for several AB weeks from biodegradable poly (DL-lactic-co-glycolic acid) (PLGA) microspheres is very important for the development of a single dose vaccine. With a view to developing such a formulation, we evaluated in the vitro release of antigenic TT from TT-containing PLGA films and microspheres stabilized with gelatin or human serum albumin. Without stabilizer, TT-containing PLGA films released low levels of antigenic TT whereas TT-containing PLGA microspheres (average size 50 microMs) released 18% of antigenic TT in 4 weeks. Inclusion of gelatin and human serum albumin increased the amount of antigenic TT released from PLGA films and microspheres. As the concentration of gelatin increased from 0.08% to 2.2% in PLGA films, release of antigenic TT also increased. Similar results were found with gelatin-stabilized TT-containing microspheres. But the significant increase by higher concentration of gelatin was on the initial burst during the first week. A concentration of 0.2% gelatin was found suitable for getting approximately 40% of antigenic TT in 4 weeks. The proportion of antigenic TT to total protein was higher during the first 2 weeks of the release studies (50% during the first week and 23% during the second week). After 2 weeks, the proportion of antigenic TT was approximately 10% for the next 2 weeks. TT-containing microspheres stabilized with gelatin and human serum albumin showed stability of antigenic TT release when these microspheres were stored at 37 degrees C for 4 weeks. Gelatin appears to be a good stabilizer for TT-containing microspheres, but further studies are

required to increase the proportion of antigenic TT beyond 2 weeks.

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FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 11:03:11 ON 25 SEP 2002
            17 S VACCINE(W) (STABILISER OR STABILIZER)
L1
             5 S INOSITOL AND ASCORBIC AND UREA
L2
             0 S L1 AND L2
L3
             5 DUP REM L2 (0 DUPLICATES REMOVED)
L4
L5
             0 S INOSITOL AND L1
             0 S L1 AND UREA
L6
            0 S L1 AND ASCORBIC
L7
         3325 S VIRUS AND UREA
L8
          333 S VACCINE AND UREA
L9
         74251 S ASCORBIC?
L10
            1 S L9 AND L10
L11
           381 S INOSITOL AND UREA
L12
             0 S VACCINE AND L12
L13
             1 S VACCINE AND ASCORBIC AND UREA
L14
            74 S LAI AND HEPATITIS
L15
            31 DUP REM L15 (43 DUPLICATES REMOVED)
L16
       513014 S STABIL?
L17
            1 S L16 AND L17
L18
         27916 S HEPATITIS(W)A
L19
L20
          4445 S LAI
L21
             0 S L19 AND L20
L22
           208 S LAI AND VACCINE
L23
           0 S L19 AND L22
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L Number	Hits	Search Text	DB	Time stamp
2	10815	LAI	USPAT;	2002/09/25 11:22
			US-PGPUB;	
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			DERWENT;	
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3	335	LAI and hepatitis	USPAT;	2002/09/25 11:22
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			DERWENT:	
			IBM_TDB	
4	22	LAI with hepatitis	USPAT;	2002/09/25 11:24
-	22	LAI With hepaticis	US-PGPUB	2002/00/20 11/0
			EPO; JPO;	
			DERWENT	
			IBM TDB	
5	0	92114998.pn.	USPAT;	2002/09/25 11:24
-		'	US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
			IBM_TDB	
6	0	85107525.pn.	USPAT;	2002/09/25 11:24
			US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
		1100	IBM_TDB	2002/09/25 11:20
-	3260	HAV or (hepatitis adj A)	USPAT; US-PGPUB;	2002/09/25 11.20
			EPO; JPO;	
			DERWENT;	
			IBM TDB	,
_	1602	HAV or (hepatitis adj A) and human adj serum adj albumin	USPAT;	2002/09/24 17:24
-	1002	I HAV OF the patition day 7 y and Hamain day octain day assurement	US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
			IBM_TDB	
1-	1491	HAV or (hepatitis adj A) and human adj serum adj albumin	USPAT;	2002/09/24 17:24
		and live and vaccine and stabilizer	US-PGPUB;	
			EPO; JPO;	
		·	DERWENT;	
		Line of the second of the seco	IBM_TDB	2002/00/24 47:25
-	1491	HAV or (hepatitis adj A) and (human adj serum adj albumin)	USPAT;	2002/09/24 17:25
		and live and vaccine and stabilizer	US-PGPUB; EPO; JPO;	
			DERWENT:	
			IBM_TDB	
_	1491	HAV or (hepatitis adj A) and (human adj serum adj albumin)	USPAT;	2002/09/24 17:25
	וטדו	and live and vaccine and stabilizer	US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
			IBM_TDB	
-	1452	HAV or (hepatitis adj A) with live with vaccine with stabilizer	USPAT;	2002/09/24 17:26
			US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
			IBM_TDB	2002/00/04 47:00
-	1449	HAV or (hepatitis adj A) with live with vaccine with stabilizer	USPAT;	2002/09/24 17:26
		with (human adj serum adj albumin)	US-PGPUB; EPO; JPO;	
			DERWENT;	
			IBM_TDB	
			I ION I DD	L

				_
-	0	(live adj virus) with (stabilizer or stabiliser) with (protect\$3 with heat adj inactivat\$3)	USPAT; US-PGPUB;	2002/09/25 09:58
			EPO; JPO; DERWENT; IBM_TDB	
	18	l (live adj virus) with (stabilizer or stabiliser)	USPAT;	2002/09/25 10:29
		( ( ( Constitution of the	US-PGPUB,	
			EPO; JPO;	
			DERWENT; IBM_TDB	
_	39	mannitol and urea and inositol and (ascorbic adj acid) and	USPAT;	2002/09/25 10:30
		(amino adj acid) and trehalose and gelatin	US-PGPUB;	
			EPO; JPO; DERWENT;	
			IBM_TDB	
-	15	mannitol and urea and inositol and (ascorbic adj acid) and	USPAT;	2002/09/25 10:33
		(amino adj acid) and trehalose and gelatin and virus	US-PGPUB; EPO; JPO;	
			DERWENT;	
			IBM_TDB	
-	25	(stabilizer or stabiliser) and (mannitol and urea and inositol	USPAT;	2002/09/25 10:32
		and (ascorbic adj acid) and (amino adj acid) and trehalose and gelatin)	US-PGPUB; EPO; JPO;	
		and goldan,	DERWENT;	
		( to this contact the contact the contact that the contact the con	IBM_TDB	2002/00/25 10:33
-	0	(stabilizer or stabiliser) with (mannitol and urea and inositol and (ascorbic adj acid) and (amino adj acid) and trehalose	USPAT; US-PGPUB;	2002/09/25 10:33
		and gelatin)	EPO; JPO;	
			DERWENT;	
	0	((live adj virus) with (stabilizer or stabiliser) ) and (mannitol	IBM_TDB USPAT;	2002/09/25 10:33
		and urea and inositol and (ascorbic adj acid) and (amino adj	US-PGPUB;	
		acid) and trehalose and gelatin and virus)	EPO; JPO;	
			DERWENT; IBM_TDB	
-	0	(live adj virus) and mannitol and urea and inositol and	USPAT;	2002/09/25 10:34
		(ascorbic adj acid) and (amino adj acid) and trehalose and	US-PGPUB; EPO; JPO;	
		gelatin and virus	DERWENT;	
			IBM_TDB	
-	7	(live adj virus) with (stabilizer or stabiliser) and human adj serum adj albumin	USPAT; US-PGPUB;	2002/09/25 10:40
		Serum auj albumm	EPO; JPO;	
			DERWENT,	
	2	(live adj virus) with (stabilizer or stabiliser) with human adj	IBM_TDB USPAT;	2002/09/25 10:35
<u> </u>		serum adj albumin	US-PGPUB;	
			EPO; JPO;	
			DERWENT; IBM_TDB	
-	0	(live adj virus) with (stabilizer or stabiliser) and (ascorbic adj	USPAT;	2002/09/25 10:42
		acid) and inositol and urea	US-PGPUB;	
			EPO; JPO; DERWENT;	]
			IBM_TDB	0000/00/07 17 17
-	0	(live adj virus) with (ascorbic adj acid) and inositol and urea	USPAT; US-PGPUB;	2002/09/25 10:42
			EPO; JPO;	
			DERWENT;	
	1	(live adj virus) and (ascorbic adj acid) and inositol and urea	IBM_TDB   USPAT;	2002/09/25 10:43
_	'	three and virus, and tascorbic and and and investor and drea	US-PGPUB;	
			EPO; JPO;	
			DERWENT; IBM_TDB	
L	1		1	<del></del>

[ <u>-</u>	50	(live adj virus) and (ascorbic adj acid)	USPAT;	2002/09/25 10:43
			US-PGPUB;	
	[		EPO; JPO;	
			DERWENT;	
			IBM_TDB	
_	9	(live adj virus) and (ascorbic adj acid) and urea	USPAT;	2002/09/25 10:46
			US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
1			IBM_TDB	
-	2	(live adj virus) and inositol and urea	USPAT;	2002/09/25 10:44
			US-PGPUB;	
	1		EPO; JPO;	
			DERWENT;	
			IBM_TDB	
-	3	(live adj virus) and inositol and (ascorbic adj acid)	USPAT;	2002/09/25 10:45
			US-PGPUB;	
	1		EPO; JPO;	
			DERWENT;	
1			IBM_TDB	0000/00/05 40:40
-	0	flavivirus adj live adj vaccine	USPAT;	2002/09/25 10:46
			US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
	_	The second secon	IBM_TDB	2002/09/25 10:47
-	0	arbovirus adj live adj vaccine	USPAT;	2002/09/25 10:47
			US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
		DNA and the analysis and the second	IBM_TDB USPAT;	2002/09/25 10:47
-	0	PIV adj live adj vaccine	US-PGPUB;	2002/03/23 10.4/
			EPO; JPO;	
	!		DERWENT;	
			IBM_TDB	
	0	PIV with (live adj vaccine)	USPAT;	2002/09/25 10:47
-	1	PIV With (live adj vaccine)	US-PGPUB;	2002/00/20 10:11
			EPO; JPO;	
	1		DERWENT:	
			IBM TDB	
_	50	PIV with vaccine	USPAT;	2002/09/25 10:48
			US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
1			IBM_TDB	
-	1076	PIV or RSV with vaccine	USPAT;	2002/09/25 10:47
	1		US-PGPUB;	
	1		EPO; JPO;	
			DERWENT;	
			IBM_TDB	
-	2	PIV with vaccine.clm.	USPAT;	2002/09/25 10:49
			US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
			IBM_TDB	2002/00/25 40:54
1 -	57	measles with vaccine.clm.	USPAT;	2002/09/25 10:54
			US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
	10	and the wife was with in site!	IBM_TDB USPAT;	2002/09/25 10:55
-	12	ascorbic with urea with inositol	USPAT; US-PGPUB;	2002/09/20 10:00
			EPO; JPO;	
			DERWENT;	
			IBM TDB	
		<u> </u>	LIBINI I DR	L

L Number	Hits	Search Text	DB	Time stamp
1	7	(live adj virus) with (stabilizer or stabiliser) and human adj	USPAT;	2002/09/25 11:33
		serum adj albumin	US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
			IBM_TDB	
2	2014	urea with (stabilizer or stabiliser)	USPAT;	2002/09/25 11:33
			US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
			IBM_TDB	0000/00/05 44.00
3	0	urea with (stabilizer or stabiliser) with vaccine	USPAT;	2002/09/25 11:33
			US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
		we will detail the same at a letting and writing and	IBM_TDB USPAT:	2002/09/25 11:35
4	1	urea with (stabilizer or stabiliser) with virus	US-PGPUB:	2002/09/23 11.33
			EPO; JPO;	
			DERWENT;	
			IBM TDB	
5	0	urea and inositol with (stabilizer or stabiliser) with virus	USPAT:	2002/09/25 11:35
3		diea and mositor with (Stabilizer of Stabilizer) with virus	US-PGPUB;	
			EPO; JPO;	
			DERWENT;	
			IBM TDB	
6	21	urea and inositol with (stabilizer or stabiliser)	USPAT;	2002/09/25 11:35
-			US-PGPUB,	
			EPO; JPO;	
			DERWENT;	
			IBM_TDB	